NEUROIMMUNOLOGY

Tracing Molecules That Make The Brain-Body Connection

A rheumatologist, Ronald Wilder has long wondered why rheumatoid arthritis symptoms so often fade during pregnancy. The obvious answer is hormones, but less clear is how hormones influence the abnormal immune attack that destroys the joints. Now, with several colleagues at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Wilder is looking to an emerging discipline, one that fuses immunology with neurobiology, endocrinology, and even psychiatry, to provide him with answers.

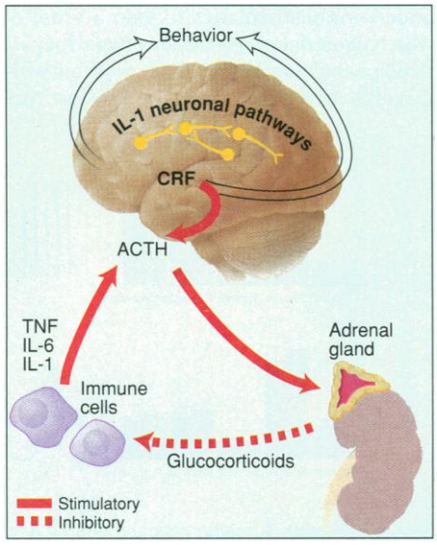
While researchers once considered the body's network of immune defenses a system unto itself, they have learned over the past 15 years that it is intimately intertwined with the nervous and endocrine systems. There are direct physical links—neurons that innervate immune organs such as the spleen and lymph nodes, for example. And now, researchers are unraveling the molecular links, which include the interleukins, originally viewed only as regulators of immune cells; neurotransmitters, once thought to act only between nerve cells; and hormones, the endocrine messengers.

As these connections come to light, they are helping to explain some previously mysterious correlations between mental and hormonal states and the immune system. Among these insights, discussed in a November 1996 meeting* at the National Institutes of Health, are how increases in corticosteroid hormones affect the immune system late in pregnancy, and how the immune system triggers specific pathways in the brain to produce the fever and fatigue that accompany infections. "We're making important advances in understanding the infrastructure of how these systems communicate and how breaking the communications can result in disease," says rheumatologist Esther Sternberg of the National Institute of Mental Health (NIMH). Ultimately, researchers say, the information may help design improved therapies for the conditions, such as better drugs for allergies and other immune reactions.

Vagus express. One set of connections leads from the immune system to the brain. Acting as what psychologist Steven Maier of the University of Colorado, Boulder, describes as a "diffuse sensory organ," the immune system relays data about incipient inflammation or new infections to the brain. The brain responds by causing a fever and the familiar tired and achy feelings that accompany infections.

Researchers had fingered certain immune regulators, primarily interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor–α (TNF-α), as the immune system's messengers to the brain, but this idea had always seemed somewhat flawed. Fevers develop within minutes of the injection of inflammatory toxins into laboratory animals—too fast for the messengers, released at the site of the injection, to achieve the high concentrations thought necessary to breach the barrier between the blood and the brain.

Then, in 1994, Maier and his colleagues



GAYKEMA, GOEHLER, WATKINS, AND MAIER, *ANNALS OF INTERNAL MEDICINE* 117, 855 (1992)

Interconnections. The brain influences immune function through hormones, particularly those in the hypothalamus-pituitary-adrenal axis, and immune messengers in turn affect the brain.

and, independently, Robert Dantzer of INRA-INSERM in Bordeaux, France, found evidence suggesting that the immune message takes a neural route to the brain. Usually, injecting immune messengers into the peritoneal cavity surrounding the gut elicits a fever in laboratory rats. But the researchers found that this doesn't happen if they first cut the vagus nerve, which extends from the brain to the kidney, liver, and other organs. "If you cut the vagus, you can block a lot of the symptoms of sickness," Maier explains.

Maier and Linda Watkins and Lisa Goehler of the University of Colorado have begun to see how the vagus might pick up the immune signals. They find that clumps of nerve cells called paraganglia, which can stimulate the vagal nerves, are triggered by IL-1 from nearby immune cells. As a result, Maier said at the meeting, the immune messenger doesn't have to travel all the way to the brain. Instead, it "acts locally" on the paraganglia, which stimulate the vagus to relay IL-1's message to the brain. But because the brain can sometimes respond to IL-1 even when the vagus has been severed, Maier says, other nervous-system pathways may be carrying this immune message as well. What's more, he adds, an initial neuronal message may subsequently be reinforced by blood-borne ones. "Immunological agents are recruiting the brain to alter behavior," making an organism tired, more sensitive to pain, or less interested in food, explains NIMH neuroendocrinologist Philip Gold.

Other researchers have found that stress, as well as inflammation, can activate parts of these same pathways. Matthew Kluger and his colleagues at the Lovelace Research Institutes in Albuquerque, New Mexico, find that simply introducing a lab mouse to a new environment can prompt an increase in IL-6, raising the body temperature and inducing typical "sickness behavior," in which the mouse loses interest in eating and exploring. In this case, though, the communication between the brain and the immune system is two-way: The brain apparently registers the stress and then activates certain immune messengers, which in turn signal the brain to cause the body to react. Ultimately, those reactions include deactivation of the immune messengers, creating a complex feedback.

Interconnections. Indeed, as researchers have known for more than a decade, the brain can shape the immune response. "It has now been shown scientifically: Mental states can influence the body's resistance to disease," says George Chrousos, an endocrinologist at the National Institute of Child Health and Human Development (NICHD).

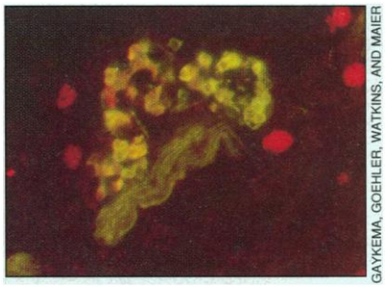
Investigators had long suspected that they act, at least in part, through the hypothalamic-pituitary-adrenal axis (HPA), which is triggered when a stress, say the sight of a potential predator, stimulates production of corticotropin-releasing factor (CRF) by the hypothalamus of the brain. Among other actions, CRF ultimately causes the release of corticosteroids from the adrenal glands. These adrenal hormones have several actions, such as providing a burst of energy by raising blood-sugar concentrations, that enable an individual to deal with a threatening or stressful stimulus.

In addition, though, the corticosteroids inhibit IL-1 production and thus reduce the inflammatory responses, an effect that is the basis of their use as anti-inflammatory drugs. In the body itself, these hormones may damp down an

* The Third International Congress of the International Society for Neuroimmunomodulation was held in Bethesda, Maryland, 13–15 November 1996.

immune response that has run its course, because the effects of IL-1 and -6 on the brain include triggering the HPA by stimulating CRF production, which creates an immune-suppressing feedback.

That damping down can have a downside, though, possibly leading to decreased ability to fight infections. At Ohio State University, Janice Kiecolt-Glaser and Ronald Glaser found that in stressed medical students, overactive HPA responses decreased the effectiveness of the hepatitis-B vaccination. Then working with immunologist John Sheridan, also from Ohio State, they found that the flu vaccine was less likely to work in people caring for spouses with Alzheimer's disease—a task known to cause a lot of stress—than in people of similar age and background not in those caretaker roles.



GAYKEMA, GOEHLER, WATKINS, AND MAIER

Close ties. Immune cells (red) stimulate the vagus nerve (seen in cross section, in green) via paraganglia cells (green and yellow).

Yet, the immune-suppressing feedback can be helpful, says NICHD's Chrousos, as it may explain the lessened rheumatoid arthritis symptoms during pregnancy. His group found that during the last trimester, the fetus produces CRF that gets into the mother's circulation and tends to make the HPA axis overly active. In addition, the estrogen increase during pregnancy may stimulate cortisol secretion. Test tube studies suggest that corticosteroid concentrations similar to those in late pregnancy suppress the cell-mediated branch of the immune system, which causes the symptoms of rheumatoid arthritis.

Conversely, there is mounting evidence that a depressed HPA axis, resulting in too little corticosteroid, can lead to a hyperactive immune system and increased risk of developing autoimmune diseases. NIMH's Sternberg and her colleagues found the first evidence for such a connection 8 years ago in studies of two strains of rats that differ in their inflammatory responses and their susceptibility to many experimentally induced autoimmune diseases. They found that Lewis rats, the sensitive strain, release much less CRF and less corticosteroid in response to stress or exposure to antigens than do the resistant Fischer rats.

Such a correlation does not necessarily prove a connection, but at the meeting, Sternberg and Barbara Misiewicz of NIMH reported that transplanting cells from the hypothalamus of embryonic Fischer rats into adult Lewis rat brains makes the recipients as unlikely to develop autoimmune disease as are the Fischer rat donors. By producing more CRF than the Lewis rat's own brain does, the transplanted tissue may prompt more vigorous HPA responses and tame the animals' hyperactive immune system.

A depressed HPA axis may contribute to an overly sensitive immune system in people, too. "The evidence is mounting that these principles apply not only in chickens, not only in rats, but also in humans," Sternberg emphasizes. For example, at the University of Trier, Germany, psychologist Angelika Buske-Kirschbaum has found that children known to suffer from atopic dermatitis—allergies that result in itchy skin and rashes—or from asthma have a blunted HPA response. When asked to tell a story or do mental math, these children show less increase in the glucocorticoid concentrations in their saliva than do their healthy peers. "They showed this very dramatic difference in the salivary cortisol response," says Sternberg. The researchers propose that the children's lower HPA function may make them susceptible to allergies in the same way it makes Lewis rats prone to autoimmune disease.

These kinds of studies, suggesting intimate links between the endocrine and immune systems and mental states, are inspiring new studies that aim to draw even tighter connections. NIMH's Gold, for example, hopes to learn how the neuroendocrine patterns of depression affect the immune system. In one form of the disease, the HPA axis is underactive, suggesting that those with this condition "may be immunologically disinhibited," he says, while in another other form, corticosteroid levels are unusually high. Ultimately, he hopes that studies of these interconnections will "provide us targets for drug treatments," Gold says, not only for depression but also for the physical symptoms associated with this condition. At the same time, his group hopes to learn whether inflammation or disease can cause depression to flare.

That holistic approach is what neuroendocrine immunology is all about, its pioneers argue. "This is the coming together of these fragmented sciences," says neuroscientist Bruce McEwen of Rockefeller University in New York City. "We're putting the body back together again."

–Elizabeth Pennisi

ATOMIC PHYSICS

Atoms Take a Turn for the Better

Every time a 747 jetliner maneuvers, patterns of light and shadow in a device called an interferometer measure the change in angle. Now, photons have a rival for sensing small rotations: interfering atoms. In the 3 February issue of *Physical Review Letters*, Massachusetts Institute of Technology (MIT) physicists describe how they used an atom interferometer, which takes advantage of the wavelike nature of matter described by quantum mechanics, to measure rotations as subtle as a quarter of a degree per hour. The paper marks a first step toward practical applications for atom interferometers, which physicists first developed in 1991.

The sensitivity of the MIT instrument is "on par with the interferometer in a 747," says Edward Smith, a member of the team that built it. And it may be just the beginning for this atom-based instrument. Because atoms have wavelengths many orders of magnitude shorter than light, he adds, "in the end, atom interferometers will be 10,000 times better than the very best commercial optical interferometers ... and probably less costly."

Like a beam of light, a beam of atoms can be split with a fine grating, sent down separate paths, and brought together again. Because of atoms' wavelike nature, the converging beams produce an interference pattern of "bright" and "dark" spots, which indicates the relative arrival times of the crests and troughs in the two beams. Anything that affects the path lengths should shift the interference pattern—and because atom wavelengths are so short, atom interferometers promise unparalleled sensitivity.

Measuring rotations was a tempting application. Interferometers can sense rotations because any twisting of the interferometer shortens one beam's path and lengthens the other, so when the waves reach the end of the device, they are no longer in phase. The phase difference—manifested in the interference pattern—shows how much the interferometer has twisted.

To realize this scheme with atoms, the MIT physicists needed exquisite vibration control and larger, finely etched gratings to control the atoms. The technology was ready a year ago, and it has now yielded a device that rivals commercial optical interferometers.

Mark Kasevich, a physicist at Stanford University, already has something even better in the works, he says: an atom interferometer that will be two orders of magnitude more sensitive than the best commercial devices. "There's a number of groups quietly trying to improve [atom interferometers]," says Steven Chu, also at Stanford. "It's getting exciting."

–Charles Seife

Charles Seife is a writer in Scarsdale, New York.